Tetrahedron Letters No.52, pp. 5261-5263, 1967. Pergamon Press Ltd. Printed in Great Britain.

STUDIES ON EPOXIDES. PART II. ABNORMAL LITHIUM ALUMINIUM HYDRIDE REDUCTION OF CIS 3,4-EPOXY-5-HYDROXYCHOLESTANES[1]

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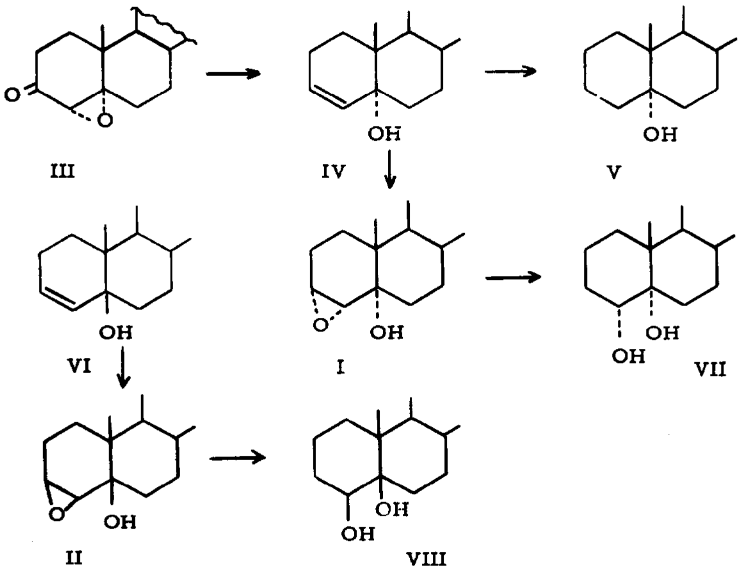
(Received in UK 12 September 1967)

As part of our studies on α-substituted epoxides we have prepared 3α,4α-epoxy-5α-hydroxycholestane (I) and 3β,4β-epoxy-5β-hydroxycholestane (II).

Hydrazine hydrate treatment of 4α,5α-epoxycholestan-3-one (III) gave the allylic alcohol (IV)*, m.p. 75-76° $[\alpha]_D$ - 12°; the two C_3 and C_4 vinylic hydrogens gave rise in the n.m.r. spectrum of IV to a narrow signal at δ 5.60; for characterisation, IV was converted into the known 5α-hydroxycholestane (V) by hydrogenation over Adams catalyst in ethanol solution. Perbenzoic acid treatment of IV proceeded stereoselectively to the 3α,4α-epoxide (I), m.p. 137-138°, $[\alpha]_D$ + 9.6°; 1-proton multiplet centered at δ 3.36 (C_3-H), and 1-proton doublet centered at δ 2.85 (J=6 cps; C_4-H).



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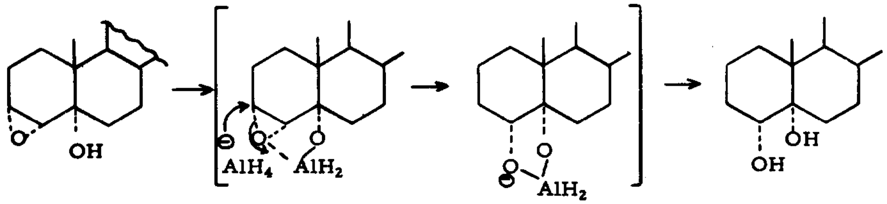
* All new compounds gave satisfactory analytical figures; molecular weights were determined by mass spectrometry; optical rotations are for chloroform solutions.

5β-Hydroxycholest-3-ene (VI) prepared by a slight modification of the procedure of Wharton and Bohlen[2] was epoxidized with perbenzoic acid to yield almost quantitatively the 3β, 4β-epoxy-derivative (II), m.p. 97-98° $[\alpha]_D$ + 55.5°; 1-proton multiplet at δ 3.39 (C_3-H) and 1-proton doublet at δ 3.01 (J=4 cps; C_4-H).

Lithium aluminium hydride reduction of the cis epoxy-alcohol I proceeded stereoselectively to yield 4α, 5α-dihydroxycholestane (VII) and, following its acetylation, the corresponding 4α-acetate, both characterised by comparison with autentic samples.[3] A similar treatment with lithium aluminium hydride of the epimeric cis epoxy-alcohol II yielded one product, namely 4β, 5β-dihydroxycholestane (VIII), also identified by direct comparison with an authentic compound[3] (the monoacetate was characterised as well in the same manner).

The formation of the two diols VII and VIII from the epoxy-alcohols I and II respectively is in contradiction with the Fürst-Plattner rule[4] of diaxial opening of epoxide rings; in both diols the hydroxy-group resulting from the cleavage of the C_3-O bond is equatorial. The same reaction performed with 3α, 4α-epoxycholestane (i.e. in the absence of the 5α-hydroxyl) proceeds by diaxial opening to yield 3α-hydroxycholestane;[5] similarly, from 3α, 4α-epoxy-7β-hydroxycholestane the 3α, 7β-dihydroxy derivative is obtained.[6]

These results may be attributed to the participation of the neighboring hydroxy-group through an intermediate of the same type as proposed[7] for the hydride reduction of α-hydroxy- and α-aminoketones.



Following the initial formation of an aluminium salt, the metal hydride ion attacks from the less hindered side, yielding after hydrolysis the vicinal diol.

Lithium aluminium hydride reduction of the isomeric 3β-hydroxy-4β, 5β-epoxycholestane yields however 3β, 5β-dihydroxycholestane[8] and not the vicinal 3β, 4β-diol as would apparently require the application of the above views. The reaction can be conceived to proceed in the same way, however the attack from the rear of the hydride ion takes place at the less hindered C_4 position leading to the sterically more favored tertiary alcohol.

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